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EXAMINER	
SAOUD, CHRISTINE J	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,067	WEINER ET AL.	
	Examiner	Art Unit	
	Christine J. Saoud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *3,6-26 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *05/05/06, 11/14/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-5 and 27, directed to peptides and pharmaceutical compositions thereof, and the election of the species of SEQ ID NO:24 in the reply filed on 05 May 2006 is acknowledged. The traversal is on the ground(s) that examination of each of the four groups of claims would not be a serious burden on the Patent Office because of their close technological relationship. This is not found persuasive because M.P.E.P. § 803 provides that the separate classification (i.e., class and subclass) of distinct inventions is sufficient to establish a *prima facie* case that the search and examination of the plural inventions would impose a serious burden upon the Examiner. MPEP (808.02) indicates that a serious burden of search can be established by separate classification of the inventions which shows that each invention has attained recognition in the art as a separate subject for inventive effort and also a separate field of search. Such separate classification was set forth in the previous Office action mailed 05 April 2006 and a *prima facie* case of serious burden of search has been established. Furthermore, Applicant has offered no evidence to rebut this showing.

Applicant further traverses the Species election requirement arguing that searching all species would not be burdensome on the Patent Office because all of the polypeptides are homologous and belong to the same protein family and they share several structural and biological features. Applicant's arguments are not persuasive because while the proteins share some structural and biological features, each

polypeptide search is distinct because each polypeptide is patentably distinct. Should Applicant like to traverse on the ground that the species are not patentably distinct, Applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the Examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention. Applicant has not asserted that the species are obvious variants or that the species are not patentably distinct. Such an admission may obviate the need for the species election.

Applicant is reminded that upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, Applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Applicant's election, with traverse, of a species of disease is noted. However, because the method claims are not rejoined, this election is premature.

The requirement is still deemed proper and is therefore made FINAL.

Claims 6-26 and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and claims 1-3 and 5 are withdrawn to the extent that they are drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 05 May 2006.

Priority

Applicant provides a reference to prior applications in both the first line of the specification and in an application data sheet (37 CFR 1.76). However, the current status of all referenced applications should also be included (i.e. abandoned, patented and the patent number, etc.).

Specification

Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

The abstract of the disclosure is objected to because it contains speculative applications not directed to the claimed invention. Correction is required. See MPEP § 608.01(b).

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The claims are not directed to therapeutic and diagnostic uses, therefore, this should not be present in the title.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-2 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims fail to include any limitations that would distinguish the claimed peptides from those which occur in nature. In the absence of the hand of man, naturally occurring proteins are considered non-statutory subject matter. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Additionally, mere purity of a naturally occurring product does not necessarily impart patentability. Ex parte Siddiqui, 156 USPQ 426 (1966). However, when purity results in a new utility, patentability is considered. Merck Co. v. Chase Chemical Co., 273 F. Supp. 68 (1967). Filing of evidence of a new utility imparted by the increased purity of the claimed invention and amendment of the claims to recite a purity limitation, if supported by the specification, is suggested to obviate this rejection. Applicant should point to the basis in the specification for any amendment to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide having the amino acid sequence of SEQ ID NO:24, or an N-terminal fragment of growth hormone consisting of approximately 135 amino acids, does not reasonably provide enablement for a genus of

anti-angiogenic peptides substantially identical to about 10-150 consecutive amino acids of human growth hormone. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification indicates that a polypeptide corresponding to the 16 kD N-terminal fragment of human growth hormone (-1 Met to Pro133 – SEQ ID NO:24), has the property of inhibiting angiogenesis (e.g. page 50 and 55-57), yet the claims encompass a vast genus of fragments of this peptide. The specification provides no examples which support the breadth of the claims, which are directed to fragments as small as about 10 amino acids and molecules which are not identical to that disclosed which are anti-angiogenic. The specification has provided no guidance as to what portion of the 16kD human growth hormone is responsible for the biological activity of being anti-angiogenic. The specification has provided no examples of mutations (other than mutation of Cys53 to Ser53) which have the required biological activity. The 16kD human growth hormone differs in biological activity from the full length human growth hormone, therefore, structurally, there is a difference which provides for this activity. Without the knowledge of what portions of the 16KD human growth hormone are responsible and critical for this activity, the skilled artisan would not be able to make peptides which are "substantially identical to about 10 to about 150 consecutive amino acids" from the N-terminal end of human growth hormone which have the required anti-angiogenic activity of the claims. Further, the skilled artisan would expect that the majority of such fragments would not work as claimed. Khurana et al. (Endocrinology

140: 4127-4132, 1999) teach that peptides of the 16kD fragment of prolactin missing the first 53 amino terminal residues lacked anti-angiogenesis activity (see for example the middle paragraph of the first column of page 4131). Prolactin and growth hormone belong to a common protein family and the 16kD fragment of prolactin and the 16kD fragment of growth hormone both possess anti-angiogenic activity. Based on the structural and functional relationship between these two proteins, one of ordinary skill in the art might expect to find a similar loss of anti-angiogenic activity in the 16kD human growth hormone as well. The specification has not provided guidance as to any correlation between the structure of the fragments and the desired function of the fragments, such that the skilled artisan could make a peptide which differed from that of the 16kD human growth hormone or the peptide of SEQ ID NO:24 and expect the required biological activity of the claims. The specification has failed to provide adequate guidance as to which of the multitude of fragments and variants encompassed by the claims such that the molecules might have the desired activity.

Therefore, due to the large quantity of experimentation necessary to generate the tremendous multitude of peptide fragments recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the requirement for a significant portion of the N-terminus of the 16kD protein for activity, and the breadth of the claims which require as few as 10 residues for

activity, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Heymsfield et al. (J. Clin. Invest. 60: 563-570, 1977) in light of Regan et al. (Proc. Nat. Acad. Sci. USA 72(5): 1684-1686, 1975).

Heymsfield et al. teach human growth hormone which has been digested with plasmin (see abstract). The result of digestion with plasmin is a human growth hormone having the amino acid structure of N-terminal amino acids 1-134 (see Regan et al. at column 1, paragraph 1). Heymsfield et al. teach pharmaceutical compositions of this human growth hormone N-terminal fragment (see page 564, column 2, under "Methods"). Heymsfield et al. is silent as to the anti-angiogenic activity of the peptide, however, this is a property that would have been possessed by the peptide of Heymsfield, and therefore, the claims are anticipated by the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heymsfield et al. in light of Regan et al. as applied above, and further in view of Tokunaga et al. (Eur. J. Biochem. 153: 445-449, 1985) and Mark et al. (U.S. Pat. No. 4,959,314).

The disclosure of Heymsfield et al. and Regan et al. are as described above. Neither reference teaches or suggests the replacement of the cysteine residue at position 53 with a serine residue (the molecule structure of the peptide of SEQ ID NO:24 of claim 4).

Tokunaga et al. teach human growth hormone which has been mutated at the cysteine residue at position 165. This cysteine residue forms a disulfide bond with the cysteine residue at position 53 in human growth hormone, creating a structure known as the large loop. Tokunaga et al. teach that elimination of this large loop structure makes the growth hormone more susceptible to plasmin hydrolysis than the intact hGH protein (see page 448, column 1, paragraph 1).

Mark et al. disclose the general strategy of replacing Cys residues known not to be essential for biological function with other amino acids in recombinant proteins (abstract). It teaches that the muteins so made will desirably tend less to form

intermolecular cross-links which could interfere with the work-up of the recombinant protein product or to form incorrect intramolecular disulfide bonds which would lower its activity (column 1, lines 39-46). It teaches that Ser is an especially favored replacement for Cys in such muteins (column 4, lines 3-11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a 16 kD N-terminal fragment of human growth hormone wherein the cysteine residue at position 53 is modified to a serine because Heymsfield et al. teach that the 16kD N-terminal fragment of human growth hormone has unique biological properties which make is use desireable and because Tokunaga et al. teach that elimination of the large loop structure in human growth hormone make the molecule more susceptible to plasmin cleavage, which would provide for a more efficient method of producing the peptide. One of ordinary skill in the art would have been motivated to modify either the cysteine residue at position 53 or the cysteine residue at position 165 because of the teachings of Mark et al. and Tokunaga et al. One of ordinary skill in the art would be further motivated to select the cysteine at position 53 because in the 16kD N-terminal fragment, this residue would be free to form undesireable intramolecular disulfide bonds, as taught in Mark et al. Therefore, the claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on Monday-Friday, 6AM-2PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CHRISTINE J. SAOUD
PRIMARY EXAMINER

Christine J. Saoud